Editorial

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Editorial for Special Issue on Ureagenesis

"These reactions [of the urea cycle] take place only in the intact liver cell… Our lack of knowledge of the chemical nature of [urea cycle] enzymes makes impossible an understanding of the chemical mechanism…, and even more remote must be the possibility of penetrating into the complex system of urea synthesis."[1] These words, written in 1934 by Sir Hans Krebs, the first to describe the reactions of the urea cycle, are part of the Preface of a book that was printed in 1976 as the proceedings of a symposium held at the University of Valencia, Spain, in 1975 on "The Urea Cycle". This book, currently only available antiquarian, still is an indispensable inspiration for all researchers in the urea cycle field as it contains extensive knowledge with still great relevance. The citation of Sir Hans Krebs was written long before the molecular bases of the respective diseases were elucidated.

The conference in 1976 was followed by another similarly prominent meeting, the International Symposium on Urea Cycle Diseases, held in September 27-29, 1981, in Okayama, Japan. Also from this event, there are proceedings published[2], which are likewise a treasure chest still in these days. However, despite the great advances in all aspects of medicine and science, and despite we nowadays deeply "penetrate into the complex system of urea synthesis", treatment of a urea cycle defect remains a challenge and complete cure is not possible.

With the two conference proceedings always in close proximity of daily work and at the same time witnessing a spectacular progress in molecular and therapeutic medicine in these days, we were inspired to organize another "International Conference on Ureagenesis Defects - Novel Models and Treatment Options", held March 19-21, 2018, in Pontresina, Engadin, Switzerland. The members of the International Scientific Committee (F. Endo, C. Harding, J. Häberle, A. Martinez, V. Rubio, S. Strom, M. Summar, and B. Thöny) have chosen "ureagenesis defects" as main focus of the conference, hereby with purpose including pathways and their disorders adjacent to and beyond the urea cycle such as Δ1-Pyrroline-5-carboxylate synthase deficiency.

This special issue of *Journal of Inherited Metabolic Disease* mirrors to some extent the wide field of ongoing research that was presented at the conference and critically discussed by the participants, but it also celebrates some key developments in the advancement for understanding urea cycle defects. A series of selected papers deals with the characterization of models, including genetic mouse models, a liver-humanized model, and 3D brain organoids. In these, Gerald Lipshutz et al. and Stephen Strom et al. focus on carbamoyl phosphate synthetase 1 deficiency (00337, 00377), Gabriella Allegri et al. on ornithine transcarbamylase deficiency (00376), and Olivier Braissant et al. on argininosuccinate lyase deficiency (00380). Today, such models are critical for the understanding of disease mechanism but also essential for testing and development of novel therapies. Pathophysiological aspects are presented by reports from Ljubica Caldovic et al. dealing with regulation of urea cycle enzymes by specific kinase signalling (00338), from Nicola Brunetti-Pierri et al. on the relationship between ammonia and autophagy (00342), from Rossella Parini et al. on energy expenditure aspects in argininosuccinate lyase deficiency (00344), from Carlo Dionisi-Vici et al. on chronic liver involvement in urea cycle defects (00016), and from Leandro Soria et al. on the effect of glutamine synthetase augmentation on ammonia detoxification (00292). Four additional articles focus on patients aspects with diagnosing, (dietary) treatment, managing adult patients, including neuropsychological aspects, and therapeutic prospects of urea cycle defects (00350, 00396, 00277, 00393). The closing paper of this special issue presents guidelines for the diagnosis and management of urea cycle disorders that should facilitate the implementation of the current knowledge for handling patients (00427).

Finally, we acknowledge the contributions by all authors and the other participants of the International Conference on Ureagenesis Defects, and hope that this collection of articles will serve the current and future generations to engage in and broaden the understanding of ammonia detoxification to develop the future arsenal for the treatment of hyperammonemia due to urea cycle defects.

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References

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